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EXAMINER	
ANGELL, JON E	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/578,900	CARULLI ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,48-60 and 62-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-60 and 62-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/9/2006 has been entered.

The amendment filed 8/9/2006 is acknowledged. The amendment has been entered. Claims 1, 2, 6, 7, 48-60 and 62-67 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/9/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

Claim 6 is objected to because of the following informalities: claim 6 has been amended such that once the cancelled material is removed from the claim, step (B) appears to duplicate the word "and". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 6, 7, 48-60 62-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 6 are drawn to a method of identifying a reagent that "**reduces** a lipid". It is noted that the specification does not appear to define the phrase "reduces a lipid". As such, the claim is given its broadest reasonable interpretation. Given the broadest reasonable interpretation, the term "reduces" renders the claim indefinite because it can have more than one meaning. Specifically, the term "reduces" can be interpreted as meaning decreasing the amount of the lipid. Alternatively, the term "reduces" can be interpreted as reducing by chemical or electrochemical means, such as by an oxidation-reduction reaction where one or more electrons are transferred from one atom or molecule to another. Since the claim can have more than one interpretation, the claims are indefinite. Claims 2, 7, 48-60 and 62-67 are included in the rejection because they are dependent claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7, 48-60 62-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

37 CFR 1.118 (a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore

specifically point out the support for any amendments made to the disclosure. (Emphasis added).

In the instant case, independent claims 1 and 6 have been amended such that they are drawn to methods of identifying reagents that reduce a lipid. The specification has been thoroughly searched, but support for the limitation "reduces a lipid" could not be found. Applicants have indicated on page 6 of the 8/9/06 communication that support for the term "reduce" could be found on page 20, lines 3-10. However, the term "reduce" does not appear in the indicated passage on page 20. It is acknowledged that page 20, lines 3-10 does have support for an "increase or decrease in the lipid level by an agent". Furthermore, "reduce" can have more than one meaning, as indicated in the rejection under 35 USC 112, second paragraph above. Therefore, the specification does not appear to have proper support for the term "reduces". Should applicants traverse this rejection, they are asked to indicate why they believe the specification provides adequate support and include specific page and line numbers which provide the required support. Claims 2, 7, 48-60 and 62-67 are included in the rejection because they are dependent claims.

Claims 2 and 7 are also separately rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2 and 7 limit the reagent of claims 1 and 6 to, among other things, an mRNA. It is noted that claims 2 and 7 are methods of identifying a reagent that reduces a lipid by first identifying a molecule (i.e., the reagent) which binds to HBM or Zmax1

nucleic acid or polypeptide. However, one of skill in the art would understand mRNAs to be nucleic acid molecules which express polypeptides which they encoded. One of skill in the art would not recognize mRNAs as agents which bind to an HBM or Zmax1 nucleic acid/polypeptide which would result in reduction of a lipid, as is encompassed by the instant claims. Furthermore, the specification does not appear to provide support for such. Should applicants traverse this rejection, they are asked indicate why they believe the specification provides adequate support and include specific page and line numbers which provide the required support.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1, 2, 6, 7, 48-60 62-67 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Claims 1, 2, 48-52, 54, 56, 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics

of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims encompass "a HBM or Zmax1" nucleic acid or polypeptide. Given the broadest reasonable interpretation of the claims consistent with the specification, the claims encompass any HBM or Zmax1 nucleic acid or polypeptide including sequences which are different than the specifically disclosed nucleic acids and polypeptides and which may also have a function that is different from the specifically disclosed sequences. That is, the claims are not limited to any specific HBM or Zmax1 sequences, therefore, given the broadest reasonable interpretation, the claims encompass HBM and Zmax1 variants which are not specifically disclosed in the specification. The specification does not appear to disclose which sequence elements of the HBM and Zmax1 sequences are critical for their function. Therefore, the specification has not adequately disclosed which sequences can be altered or deleted without disrupting the function of the sequence. Accordingly, in the absence of sufficient recitation of

distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

In this case, the skilled artisan cannot readily envision the detailed chemical structure of the variant HBM and Zmax1 sequences such that the functional sequence could be readily distinguished from the non-functional sequences. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only the HBM and Zmax1 sequences specifically disclosed in the specification meet the written description provision of 35 U.S.C. §112, first paragraph.

Claim 52 is also separately rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics,

structure/function correlation, methods of making the claimed product, or any combination thereof.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Claim 52 encompasses a known ligand for HBM or Zmax1 nucleic acid and polypeptide sequences. Therefore, the claims encompass a genus that includes any ligand that binds to HBM or Zmax1 sequences. However, the specification only discloses one specific known ligand: ApoE. No other ligands encompassed by the claims can be found in the specification or in the prior art. Since the specification and prior art only teach one species (ApoE) of the claimed genus, the specification does not provide adequate written description of the claimed genus.

In this case, the skilled artisan cannot readily envision which molecules would be HBM or Zmax1 ligands without performing additional experimentation. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only the ligand that is ApoE meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 101 and 112, 1st paragraph combined

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7, 48-60 and 62-67 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility.

The instant claims are drawn to a method for identifying a reagent that reduces a lipid comprising identifying a molecule that binds to HBM or Zmaxl nucleic acid or polypeptide and administering the reagent to an animal or cell and determining if the reagent reduces said lipid (e.g., see claims 1 and 6)

When considering the utility of the instant claims, the issue is not merely whether Zmax1 and HBM have utility in and of themselves, but whether the claimed methods of identifying molecules that reduce a lipid have utility under 35 U.S.C. § 101. To be clear, the issue is whether or not methods of identifying a reagent that binds to HBM or Zmax1 nucleic acid or polypeptide and further determining if this reagent reduces a lipid has credible, substantial and specific or well-established utility.

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification. The specification clearly asserts that the claimed methods have utility for identifying molecules involved in lipid regulation. The specification, as well as the prior art indicate, indicates that lipids are involved in many important biological processes. Furthermore, it is recognized that an aberrant serum lipid levels is associated with disease. For instance, aberrantly high levels of serum lipids has been associated with atherosclerosis and other various diseases. Since identifying molecules associated with disease is credible, the asserted utility for the claims is credible.

The second issue is whether substantial and specific utilities are disclosed in the specification. As indicated above, the specification must assert substantial AND specific utility for the claimed methods. With respect to "specific" utility, MPEP 2107.01 states,

A "specific utility" is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. Office personnel should distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful. For example, indicating that a compound may be useful in treating unspecified disorders, or that the compound has "useful biological" properties, would not be sufficient to define a specific utility for the compound. Similarly, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA

target. A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. Contrast the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the latter category are sufficient to identify a specific utility for the invention. Assertions that fall in the former category are insufficient to define a specific utility for the invention, especially if the assertion takes the form of a general statement that makes it clear that a "useful" invention may arise from what has been disclosed by the applicant. Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (CCPA 1973).

The regulation of serum lipid levels is recognized in the art as a very complex process that involves not one single factor, but many different factors including diet as well as the function of many different genes. For instance, Ye et al. (Am. J. Clin. Nutr. 2000; Vol. 72 (Suppl), pages 1275S-1284S; previously cited) teaches that genes influence quantitative variations in plasma lipoprotein concentrations (see abstract). Specifically, Ye reviews a number of DNA sequence polymorphisms (specifically, polymorphisms in the genes encoding ApoA-I, ApoA-IV, ApoB, ApoC-III, ApoE, LPL, CETP, LCAT, and LDL receptor) which are thought to be involved in plasma lipid regulation. Therefore, Ye teaches that regulating serum lipid levels is a complex process that involves many different biological and biochemical factors and processes including diet as well as the activity of at least 9 specific gene products.

Therefore, it is clear that "lipid regulation" is not limited to a single process but encompasses the involvement of many different biological and biochemical factors and

processes. As such, the assertion that the method has utility for identifying molecules involved in lipid regulation is not a specific utility.

It is acknowledged that the specification asserts that Zmax1 and HBM are members of the LDL receptor family, based on sequence similarity alone. The specification also asserts that HBM and Zmax1 are "involved in lipid regulation". However, the specification does not disclose how Zmax1 and HBM are specifically involved in lipid regulation.

Furthermore, the claimed methods do not have a specific utility because the HBM and Zmax1 molecules used in the instant methods could be substituted with any molecule and the method could still be used to identify molecules that reduce lipids. That is, the instant claims are not specific because the methods could be practiced using any molecule, not just HMB or Zmax1.

With respect to "substantial" utility, MPEP 2107.01 states,

A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that

require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities": ...

(C) A method of assaying for or identifying a material that itself has no specific

and/or substantial utility;

In the instant case, the claimed invention is not considered a substantial utility because additional experimentation would be required in order to determine that the identified molecules which bind to HBM or Zmax1, as well as HBM and Zmax1 themselves, are actually involved in reducing a lipid.

The last consideration is whether there is a well-established utility for the claimed invention. The specification and relevant art do not appear to disclose any "well-established" established utilities for the claimed method of identifying molecules involved in reducing a lipid using Zmax1 and HBM.

Regarding the involvement of HBM in lipid regulation, the specification discloses that biochemical tests were performed to measure the serum levels of various lipid containing molecules and precursors in affected and unaffected HBM family members to test whether HBM affects lipid regulation (see Example 3, starting at p. 125). The specification discloses that HDL levels are "generally higher in affected males than unaffected males" (see p. 126, line 21-27).

Regarding Zmax1's involvement in lipid regulation, there does not appear to be any data presented indicating the any particular lipid profile with Zmax1. The basis of

Zmax1 involvement in lipid regulation appears to be based on the sequence similarity of Zmax1 with LDL-receptors and its similarity to HBM.

However, neither the specification or the art of record teaches how HBM and Zmax1 are specifically involved in lipid regulation. Therefore, at best, Applicants have identified an association between a specific polymorphism (HBM) and a specific lipid profile without disclosing how HBM, let alone Zmax1, is involved in determining lipid levels. Since the function of HBM and Zmax1 has not been identified, further experimentation would be necessary in order to determine how HBM and Zmax1 are involved in lipid regulation before the claimed methods can be considered specific and substantial.

In conclusion, the claimed invention must be supported by a specific and substantial asserted utility or a well-established utility. The claimed invention is drawn to method of identifying reagents that reduce a lipid wherein the methods rely on identifying molecules which bind to HBM or Zmax1 sequences.

Claims 1, 2, 6, 7, 48-60 and 61-67 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7, 48-60 and 61-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for identifying reagent that reduce a lipid by identifying molecules that bind to Zmax1 or HBM. Therefore the nature of the invention is a biological assay to identify molecules that reduce a lipid wherein said molecules exert their effect either directly or indirectly through Zmax1 or HBM.

The unpredictability of the art and the state of the prior art

The art of record clearly indicates regulating the level of a lipid (e.g., increasing or decreasing lipid levels) is a complex process that involves the action of many different

genes as well as other factors such as diet. Specifically, Ye et al. (Am. J. Clin. Nutr. 2000; Vol. 72 (Suppl), pages 1275S-1284S; previously cited) teaches that genes influence quantitative variations in plasma lipoprotein concentrations (see abstract). Specifically, with respect to plasma lipid levels, Ye reviews a number of DNA sequence polymorphisms (specifically, polymorphisms in the genes encoding ApoA-I, ApoA-IV, ApoB, ApoC-III, ApoE, LPL, CETP, LCAT, and LDL receptor) which are thought to be involved in plasma lipid regulation. Therefore, Ye teaches that regulating serum lipid levels is a complex process that involves many different biological and biochemical factors and processes including diet as well as the activity of at least 9 specific gene products.

Therefore, it is clear that "lipid regulation" is not limited to a single process but encompasses the involvement of many different biological and biochemical factors and processes.

Additionally, in order for the method to be able to identify molecules involved in lipid regulation, it is imperative that HBM and Zmax1 are specifically involved lipid regulation. The specification discloses that HBM and Zmax1 are LDL-receptor family members, based on sequences similarity to known LDL-receptors as well as the association of the HBM polymorphism with a particular lipid profile. There is no disclosure in the specification which indicates either HBM or Zmax1 is a functional LDL receptor that is directly involved in lipid regulation.

Furthermore, the relevant art at the time of filing recognized that LDL-receptors could be involved in functions other than lipid regulation. For instance, Willnow et al. (Nature Cell Biol.; Vol. 1, October 1999, pages E157-E162) teaches,

> "Lipoprotein receptors used to be viewed simply as the means by which cells were supplied with lipids for energy production and membrane synthesis. This perception has now changed dramatically. Megalin, a member of the low density lipoprotein receptor gene family, turns out to mediate the endocytic uptake of retinoids and steroids, thus helping to regulate their biological function. Other members of this receptor family interact with cytosolic signaling proteins, giving this evolutionary ancient family of receptors and entirely unexpected new role as transducers of extracellular signals." (See abstract, emphasis added).

Therefore, the prior art teaches that LDL-receptors (which appellants assert includes Zmax1 and HBM) can be involved in processes other than lipid regulation, such as endocytic uptake of retinoids and steroids. Since the LDL receptor is known to be involved in processes other than lipid metabolism, one of ordinary skill in the art would not be able to associate Zmax1 with LDL regulation based on sequence similarity alone.

Finally, the art also teaches that gene association studies are typically wrong. For instance, Lucenti (The Sceintist, 2004; Vol. 18(24), page 20) teaches:

> "The first published study linking gene to disease is often far from the last word on the subject... Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only a is only roughly a one third chance that studies will reliably confirm the finding."

Therefore, the mere association of HBM with a particular profile does not conclusively indicate that HBM or Zmax1 cause that specific lipid profile nor does it indicate how they specifically affect the lipid profile. Therefore, further experimentation is necessary.

In view of the totality of the prior art, it is clear that a mere observation that HBM may be associated with a particular lipid profile and that HBM and Zmax1 are members of the LDL receptor family of proteins is not sufficient to establish that HBM and Zmax1

are directly involved in lipid regulation, which is required in order for the claimed methods to have utility and to be fully enabled.

Working Examples and Guidance in the Specification

The specification asserts that Zmax1 and HBM are LDL-receptor family members involved in lipid regulation. The specification asserts that Zmax1 is involved in lipid regulation based on alignments alone. The specification also asserts that HBM is involved in lipid regulation based on sequence similarity as well as the association of the HBM polymorphism with a particular lipid profile. For example, Example 3 in the specification discloses,

> "Since Zmaxl has similarity to the LDL receptor family of genes, it may be involved in lipid metabolism. However, others have reported that lipid profile variables did not show significant association with bone mass and could not be used as indicators for bone mineral density (Zabaglia et al., "An exploratory study of association between lipid profile and bone mineral density in menopausal women in a Campinas reference hospital," Cad. Saude Publica 14: 779-86 (1998)). (Emphasis added)
>
> "To test whether the HBM gene was involved in lipid regulation, biochemical tests were performed to measure serum level of various lipid containing molecules or precursors in affected and unaffected HBM family members to test whether the HBM mutation in the Zmaxl gene effects lipid metabolism... The results obtained were statistically significant: (1) Triglyceride levels were generally lower in affected individuals than in unaffected individuals, and (2) very low density lipoprotein (VLDL) levels were generally lower in affected individuals than in unaffected individuals. Additionally, the following comparisons approached statistical significance (p=0.06): (1) high density lipoprotein (HDL) levels were higher in affected males than in unaffected males, and (2) the ratio of low density lipoprotein (LDL) to high density lipoprotein (HDL) was generally higher in affected males than in unaffected males." (See p. 126, lines 4-27).

Here, Applicants indicate the Zmax1 has "similarity" to the LDL receptor family of genes, but it is not clear exactly how similar Zmax1 is to the LDL receptors. Applicants acknowledge that the prior art had not made a connection between lipid

metabolism and bone mineral density. In this Example, Applicants try to associate the HBM gene with lipid metabolism by evaluating the serum levels of some lipid containing molecules in individuals with and without HBM. The only statistically significant data disclosed indicates the individuals having the HBM polymorphism also have generally lower triglycerides levels and generally lower VLDL levels compared to individuals without HBM.

In contrast to the above disclosure, Zabaglia (1998, previously cited) teaches that HDL levels showed an inverse correlation to bone mass in postmenopausal women to a very high degree of statistical significance, indicating that as bone mass increases HDL decreases (while the specification indicates males having high bone mass had increased HDL levels). The only apparent differences between to two data sets is that the specification was analyzing HDL levels in men with high bone mass and Zabaglia was analyzing 1HDL levels in postmenopausic woman. It is not clear why the association of HBM with HDL is not consistent between the two groups, bringing into question association of HBM with lipid regulation.

The specification does not provide any working examples wherein the claimed method was used to positively identify a molecule involved in lipid regulation.

Quantity of Experimentation

Additional experimentation would be required in order to first establish that HBM and Zmax1 are involved in lipid regulation. This would additional experimentation to identify which biochemical process/processes of lipid regulation HBM and Zmax1 are involved in as well as identify how Zmax1 and HBM were specifically "involved" in lipid regulation. Once these molecules were identified, additional further experimentation

would be required in order to determine which of the molecules actually caused HBM or Zmax1 to reduce the lipid levels in the animal or cell.

Level of the skill in the art

The level of the skill in the art required to practice the claimed method is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the instant claims. Therefore, additional experimentation is required before one of skill in the art could make and use the claimed invention as indicated. The amount of additional experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

Applicant's arguments filed 8/9/06 have been fully considered.

Applicants argue that the specification and art indicate that HBM and Zmax1 genes are involved in lipid regulation and that Zmax1 binds ApoE. Applicants argue that this demonstrates that LRP5 has a role in mediating lipid levels. Applicants also provide two new references (Guo et al. and Suwazono et al.) in support of their position.

The assertion that the Zmaxl and HBM are "involved" in lipid regulation does not impart a specific and substantial utility for HBM and Zmaxl because the mere observation that Zmaxl and/or HBM is "involved" in lipid regulation does not indicate "how" they involved in the process. Thus, additional experimentation would clearly be required in order to determine how HBM and Zmaxl are involved in the process of lipid modulation. Additionally, the literature of record has been fully considered, and it is acknowledged that the post-filing literature supports Applicants' assertion that Zmaxl (LRP-5) may be involved in lipid regulation. However, merely observing that Zmaxl may be involved in lipid regulation does not establish a specific and substantial utility for Zmaxl, and it does not establish utility for HBM, which is a variant of Zmaxl. The Guo et al and Suwazono et al references have been fully considered. However, neither reference indicates the function of HBM or Zmax1 nor do they disclose how HBM and Zmax1 are involved in regulating lipids levels. The newly cited reference only support applicants disclosure that HBM and Zmax1 may have a role in lipid regulation. Furthermore, the claims must be enabled by the specification at the time of filing. Therefore, even if the references provide insight into the function of HBM and Zmax1 function, the specification, at the time of filing does not provide an enabling disclosure for the claimed invention.

Applicants argue that the facts of the instant case are different from those of In Re Fischer because in Fisher ESTs were used in the assays to identify polymorphism in plants wherein the polymorphisms would have no characterized feature, while the claimed methods utilize fully isolated sequences which have been genetically analyzed.

This is not persuasive because although HBM and Zmax1 have been genetically analyzed, at best the analysis provide indicates an association of HBM to bone mass and a particular lipid profile. The specification and art of record do not indicate teach the specific function of HBM or Zmax1, therefore further experimentation is required in order to determine how HBM and Zmax1 function in regulating lipid levels. As such, the instant claims would identify a reagent which binds to Zmax1 or HBM and then further analyze the reagent to determine if the reagent reduces a lipid in an animal or cell. Therefore, the methods of using HBM and Zmax1 sequences to identify a reagent that reduces a lipid do not have specific and substantial utility.

Applicants argue that the method of screening is enabled because all of the reagents were known or are provided and the binding assays and assays for determining lipid changes were known at the time.

In response, the issue is not whether or not all of reagents and the methods of determining binding and lipid levels were known in the art. The issue is whether or not the specification provides an enabling disclosure for a method of identifying a reagent that reduces a lipid wherein the method relies on identifying a reagent that binds to HBM or Zmax1 and further determining if the reagent also reduces a lipid in an animal or cell. Therefore applicant's arguments are not persuasive.

Applicants argue that further experimentation would not be required in order to make and use the claimed method.

In response, it is respectfully pointed out that the function of HBM and Zmax1 are not disclosed. Therefore, it is not clear how HBM or Zmax1 function in regulating lipid levels. Therefore, the claimed methods would require further experimentation to

determine how HBM and Zmax1 are involved in lipid regulation in order to enable the claimed method.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. D. Schultz, who can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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